General

Guideline Title

Evidence based clinical practice guideline for management of EBV-associated post-transplant lymphoproliferative disease (PTLD) in solid organ transplant.

Bibliographic Source(s)

Cincinnati Children's Hospital Medical Center. Evidence based clinical practice guideline for management of EBV-associated post-transplant lymphoproliferative disease (PTLD) in solid organ transplant. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2012 Jan. 18 p. [110 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Cincinnati Children's Hospital Medical Center. Evidence based clinical practice guideline for management of EBV-associated post-transplant lymphoproliferative disease (PTLD) in solid organ transplant. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2011 Jun. 18 p. [103 references]

Recommendations

Major Recommendations

The strength of the recommendation (strongly recommended, recommended, or no recommendation) and the quality of the evidence (1a-5) are defined at the end of the "Major Recommendations" field.

An algorithm for the evaluation and initial management of solid organ recipients and therapeutic intervention is presented (see Post-Transplant Lymphoproliferative Disease [PTLD] Evaluation algorithm in the original guideline document). Initial assessment begins in the patient with detectable Epstein Barr virus deoxyribonucleic acid (EBV DNA) typically found during surveillance of peripheral blood but may begin in the patient with concerning clinical symptoms. Radiographic assessment is dictated by clinical symptoms with surgical intervention for diagnostic biopsy or resection when a mass lesion is detected. When lymphoproliferation is not detected immunosuppression is continued with monitoring of the patient for PTLD. Antiviral therapy for EBV is considered if not already in use. Although the diagnosis of PTLD requires supportive histologic findings, some patients may initially be too ill for surgical evaluation or biopsy. In such cases a presumptive diagnosis of PTLD may be made, empiric therapy initiated, and confirmational biopsy performed when patient is thought able to safely endure invasive procedure.

An algorithm for the treatment of EBV-associated PTLD is presented (see Treatment Algorithm for EBV-Associated PTLD in the original guideline document). In patients with EBV, calcineurin inhibitor immunosuppression is reduced according to the health of the allograft. Calcineurin inhibitors are stopped in patients failing to adequately respond to reduced immunosuppression and in patients whose allograft health allows it. These patients receive further therapy with rituximab or chemotherapy initiated depending upon the clinical status as described below:

- Rituximab for patients minimally ill, without evidence of graft rejection, having polymorphic histology and small mass lesions
- Low dose chemotherapy with rituximab for patients with monomorphic histology, a large mass lesion, fulminant PTLD or evidence of graft rejection
- Conventional dose chemotherapy for patients with Burkitt lymphoma and those failing to respond to low dose chemotherapy.

1. It is recommended that confirmation of PTLD be based on the combination of compatible virologic, clinical, pathological and radiologic findings (Local Consensus [5]).

Evaluation

Laboratory Screening and Monitoring

2. It is recommended that serum EBV Viral Capsid Antigen immunoglobulin G (VCA IgG) and Immunoglobulin M (IgM) antibodies be obtained and evaluated in the recipient and donor at the time of transplantation to assess risk (see Table 1 in the original guideline document) (Walker et al., 1995 [3a]; Aris et al., 1996 [4a]; Ho et al., 1988 [4a]; Local Consensus [5]).
3. It is recommended that all patients be monitored for evidence of increased EBV-induced B-cell proliferation or EBV reactivation (McDiarmid et al., 1998 [3b]) by measuring blood quantitative EBV polymerase chain reaction (PCR) at regular intervals after transplantation (see Table 2 in the original guideline document). The time intervals and duration of monitoring may vary depending on identified risk factors (Local Consensus [5]).
   Note 1: What is clearly and consistently concluded from most studies is that monitoring of EBV copy numbers in the blood is useful in managing the patients and alerting the clinicians to the possible development of PTLD. Monitoring also helps in developing a plan for managing patients with this complication (Meerbach et al., 2008 [3a]; Sebelin-Wulf et al., 2007 [3b]; Cesaro et al., 2005 [3b]; Rowe et al., 1997 [3b]; Rogers et al., 1998 [4a]; Piriou et al., 2004 [4b]; Groen & Witte, 2001 [4b]; Stevens et al., 2002 [5]; Local Consensus [5]).

   Controversy still remains regarding:

   - EBV DNA threshold levels
   - Significance of chronic EBV DNA detection
   - Need and timing for intervention in the case of isolated EBV DNA detection (Lee et al., 2005 [3a]; Schubert et al., 2009 [3b]; Inomata et al., 2005 [4a]; Holmes et al., 2002 [4a]; D'Antiga et al., 2007 [4b])

   Note 2: It is clear that, although monitoring of blood levels of EBV copies can be useful in recognizing patients who are at risk for PTLD, it does not exclude the possibility of patients developing PTLD in the absence of any concomitant EBV DNA detection in blood. This is particularly true in patients who have been treated with anti CD-20 antibodies (Local Consensus [5]).

   Note 3: There is ongoing controversy over whether plasma values for EBV are more predictive than whole blood values (Kullberg-Lindh et al., 2008 [4a]; Fafi-Kremer et al., 2004 [4a]).

   The quantitative PCR assay used at Cincinnati Children's Hospital Medical Center is a whole blood assay that specifically amplifies the region of the EBV genome that encodes nuclear antigen (EBNA) (Groen & Witte, 2001 [4b]; Local Consensus [5])

   Note 4: PCR values are dependent upon the assay used, therefore caution must be used in comparing PCR values between laboratories (Preiksaitis et al., 2009 [4b])

Clinical Assessment of PTLD

Compared to adult recipients, more PTLD cases occur in the first post-transplant year in the pediatric population and are associated with concomitant EBV DNA detection in blood, and B-cell lineage (Dharnidharka & Araya, 2009 [5]). No symptom is pathognomonic for PTLD. Therefore, a high index of suspicion and clinical vigilance must be maintained at all times, allowing for timely evaluation and intervention for PTLD. The transplanted organ is often but not always involved in the lymphoproliferation.

4. It is recommended that a high index of suspicion be maintained for PTLD in all solid organ transplant patients:
   - Most frequently reported clinical findings and symptoms of PTLD are:
     - Lymph node enlargement, lymphadenopathy, splenomegaly (33%) (Cacciarelli et al., 1998 [3a]; Harwood et al., 1999 [3b]; Srivastava et al., 1999 [3b]; Cao et al., 1998 [4a]; Dharnidharka & Araya, 2009 [5]; Green et al., 1999 [5]; Markin, 1994 [5])
     - Abdominal symptomatology (29%) (Dharnidharka & Araya, 2009 [5]) gastrointestinal (GI) disturbances - diarrhea, abdominal pain, GI bleeding, vomiting, anorexia, protein losing enteropathy, weight loss, intestinal ulcers, or bowel obstruction/perforation (Cacciarelli et al., 1998 [3a]; Smets et al., 2000 [3b]; Sarkar et al., 2006 [4a]; Webber et al., 2006

[4a]; Cao et al., 1998 [4a]; Shapiro et al., 1988 [4b]; Green et al., 1999 [5]; Kingma et al., 1996 [5]; Cohen, 1991 [5])
- Allograft dysfunction (11%) (Quintanilla-Martinez et al., 2000 [3b]; Randhawa et al., 1996 [4b]; Dharnidharka & Araya, 2009 [5])
  Note: Allograft dysfunction may often be mistaken for rejection (Local Consensus [5])

- Central nervous system (CNS) related symptoms (11%) (Dharnidharka & Araya, 2009 [5]).

- Other symptoms may include:
  - Fever - the most frequently reported symptom, alone or with other symptoms (Cacciarelli et al., 1998 [3a]; Quintanilla-Martinez et al., 2000 [3b]; Smets et al., 2000 [3b]; Harwood et al., 1999 [3b]; Srivastava et al., 1999 [3b]; Cao et al., 1998 [4a]; Shapiro et al., 1988 [4b]; Green et al., 1999 [5]; Markin, 1994 [5])
  - Hypotension or septic-like syndrome
  - Genitourinary (GU) or gynecological (GYN) disturbances - renal or ovarian dysfunction, vaginal bleeding (Local Consensus [5])
  - Tonsillar hypertrophy, upper respiratory obstruction/sleep apnea (Cacciarelli et al., 1998 [3a]; Broughton et al., 2000 [4a]; Cao et al., 1998 [4a]; Lattyak et al., 1998 [4b]), adenoidal hypertrophy (Srivastava et al., 1999 [3b])
  - Infectious mononucleosis syndrome - sore throat, fatigue, anorexia, headache (Broughton et al., 2000 [4a]; Markin, 1994 [5]), rash (Cao et al., 1998 [4a])
  - Hepatic or splenic enlargement (Quintanilla-Martinez et al., 2000 [3b]; Smets et al., 2000 [3b]; Green et al., 1999 [5])
  - Anemia, cytopenia, hemophagocytosis, hemolysis (Quintanilla-Martinez et al., 2000 [3b]; Okano & Gross, 1996 [5])
  - Respiratory symptoms - shortness of breath, cough, upper airway obstruction (Webber et al., 2006 [4a])
- A PTLD clinical checklist is included (see Addendum in the original guideline document) for a list of possible clinical manifestations of PTLD

Diagnosis of PTLD

Tissue Analysis

5. It is recommended that a biopsy of the involved organ/site be performed once symptoms of PTLD are identified. The use of the World Health Organization (WHO) criteria may be considered for biopsy, assessment, and evaluation (Local Consensus [5]; Harris et al., 1999 [5a]) (see Table 3 in the original guideline document).
   Note 1: Some patients may initially be too ill for surgical evaluation or biopsy.

   Note 2: Patients can have different histology and clonality at different sites of disease (Chadburn et al., 1995 [5]).

6. It is recommended that in situ hybridization for EBER (Epstein Barr encoding ribonucleic acid [RNA]) be performed on the biopsy specimen (Local Consensus [5]).
7. It is recommended that additional diagnostic tests be conducted to determine the extent of disease once diagnosis of PTLD is confirmed:
   - Bone marrow biopsy, indicated if cytopenias, lymphocytosis, or lymphoblasts in the peripheral blood
   - Lumbar puncture, indicated by central nervous system signs/symptoms
   - Endoscopy indicated if gastrointestinal or pulmonary symptoms are present
   - Radiologic evaluation (described below)

   (Local Consensus [5])

Radiologic Testing

There is insufficient published evidence for the use and value of imaging in asymptomatic EBV viremia. The recommendations in this section are based on studies that used either a surveillance transplant protocol or the presence of clinical symptoms to direct imaging.

8. It is recommended that the use of radiographic imaging for PTLD screening be limited to patients with clinical symptoms or detectable EBV DNA in the blood; this is due to the lack of specificity and sensitivity of radiologic studies for PTLD (Donnelly et al., 1998 [4a]; Dodd et al., 1992 [4a]; McCormack et al., 2006 [4b]; Pickhardt & Siegel, 1999 [4b]; Pickhardt et al., 1998 [4b]).
9. It is recommended to image the head, sinuses, neck, chest, abdomen, and pelvis only when PTLD is suspected, to detect the full extent of organ involvement (Roy, Vivero, & Smith, 2008 [4a]; O'Conner & Franc, 2005 [4a]; Dodd et al., 1992 [4a]; Marom et al., 2004 [4b]; Pickhardt & Siegel, 1999 [4b]).
10. It is recommended that contrast enhanced computed tomography (CT) be used for primary evaluation if PTLD is detected. Chest radiographs, ultrasound, magnetic resonance imaging (MRI), and 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) have been used to detect PTLD, but best serve as non-invasive follow up tools, and targeted first line tools for specific organs (Maturen et al.,

2004 [4a]; Donnelly et al., 1998 [4a]; Dodd et al., 1992 [4a]; Riebel, Kebelmann-Betzing, & Scheer, 2007 [4b]; von Falck et al., 2007 [4b]; McCormack et al., 2006 [4b]; Lopez-Ben et al., 2000 [4b]; Pickhardt et al., 1998 [4b]).
Note 1: With the exception of PET, these imaging modalities provide morphologic evaluation only. PET provides functional rather than morphologic information with increased signal on PET scanning reflecting increased metabolic activity. Limited data suggest that PET scanning is a sensitive means of detecting PTLD and that it may provide complimentary information to CT or MRI (O'Conner & Franc, 2005 [4a]; von Falck et al., 2007 [4b]; Marom et al., 2004 [4b]).

Note 2: Limited PET sensitivity in detecting mucosa associated lymphoid tissue (MALT) lymphoma suggests that PET scanning may be less sensitive in less aggressive types of PTLD. (Hoffman et al., 1999 [3b]; Perry et al., 2007 [4b]).

Note 3: CT scanning detects more thoracic disease than chest radiographs (Dodd et al., 1992 [4a]; Pickhardt et al., 1998 [4b]).

Note 4: Lung parenchyma cannot be evaluated with ultrasound (Herth & Becker, 2003 [5]), MRI evaluation of the lung parenchyma is limited (Hirsch et al., 2008 [5]; Local Consensus [5]).

Note 5: Caretakers need to be aware of the ongoing risk of high cumulative doses of radiation and contrast material from imaging studies performed for the detection and treatment of PTLD (Brenner, 2010 [5]; Robbins, 2008 [5]; Local Consensus [5]).

PTLD Management

Preventive Treatment

11. It is recommended to adopt in all solid organ transplant recipients clinical vigilance and close clinical monitoring for possible onset of tissue involvement or systemic symptoms. (Local Consensus [5]).
12. It is recommended that patients with detectable EBV DNA in blood and no clinical symptoms be maintained within protocol range of immunosuppression levels (Local Consensus [5]).
    Note: Reduction of immunosuppression from standard protocols at this stage is controversial (Schubert et al., 2008 [4a]; Dharnidharka & Araya, 2009 [5]).
13. It is recommended to consider antiviral agents (e.g., ganciclovir, valganciclovir, acyclovir, or cidofovir) for asymptomatic patients with detectable blood EBV DNA (Local Consensus [5]).
14. It is recommended to consider on an individual case basis the use of rituximab in patients with detectable EBV DNA in their blood and who are at high risk for rejection with low immunosuppression (e.g., multivisceral transplant patients and heart transplant patients) (Local Consensus [5]).

PTLD Treatment

The wide clinical spectrum of PTLD necessitates that therapy be individualized based upon the histological findings and clinical setting. Observational studies consistently imply that decreased immunosuppression is associated with regression of PTLD. Beyond reduction of immune suppression, the optimal management of EBV disease and PTLD in solid organ transplant recipients is controversial. Antiviral agents inhibit EBV deoxyribonucleic acid replication *in vitro* and *in vivo*, however there is inconclusive data regarding their efficacy in the treatment of PTLD in the pediatric population. Similarly, there is inconclusive data supporting the use of intravenous immunoglobulin (IVIG), cytomegalovirus (CMV)-hyperimmune globulin in the treatment of PTLD. Surgical resection is beneficial when a complete resection can be safely accomplished. Other therapeutic modalities include immunotherapy with the anti-CD20 monoclonal antibody (rituximab) and both low-dose and conventional dose chemotherapy. Therapy with autologous EBV stimulated cytotoxic T-cells has shown benefit in early clinical investigations but is not widely available for clinical use (Heslop et al., 2010 [3a]; Gross et al., 2005 [3a]; Orjuela et al., 2003 [3b]).

PTLD Staging and Disease Monitoring

15. It is recommended that patients with PTLD be appropriately staged for the extent of their disease and subsequently monitored using physical exam, laboratory, radiological, and pathological evaluations for evidence of persistent, progressive or recurrent PTLD as well as allograft rejection (Local Consensus [5]).

Reduction of Immunosuppression

16. It is recommended that calcineurin inhibitors (CNI) be decreased from transplant protocol range in patients following the diagnosis of PTLD whenever possible (Local Consensus [5]).
    Note 1: In the first year post-transplantation, decrease the dose of CNI to achieve trough levels, one-third the target transplant protocol range for patients without PTLD (Local Consensus [5]). After the first year post-transplantation, decrease CNI daily dose by half.

Note 2: It is important to take into account the relative risk of morbidity and/or mortality due to rejection, secondary to decreased immunosuppression for each specific organ type and patient (Local Consensus [5]).

17. It is recommended to avoid use of:
    a. Anti-T cell monoclonal antibodies when possible in patients with PTLD (Local Consensus [5])
    b. Alpha-interferon as a first line therapy due to concerns of toxicity and availability of newer agents (Local Consensus [5])

Surgical Resection

18. It is recommended that surgical resection of tumor masses be performed when a complete resection can be obtained with low risk of morbidity (Local Consensus [5]).

Rituximab

19. It is recommended that rituximab treatment be considered in high risk patients at the same time immunosuppression is being reduced. High risk patients include patients at high risk for rejection with lower immunosuppression (e.g., multivisceral transplant patients and heart transplant patients) (Local Consensus [5]).
20. It is recommended to treat with rituximab patients with evidence of persistent or progressive PTLD, in the absence of allograft rejection (Local Consensus [5]).

    Note 1: Usual dosing of rituximab is 375 mg/m^2 weekly for 4 weeks (Choquet et al., 2006 [3a]; Genetech, 2010 [5b]).

    Note 2: Extended administration for an additional 4 weeks may be considered in patients achieving a partial response (Gonzales-Barca et al., 2007 [3a]).

    Note 3: Premedication is encouraged to decrease incidence of infusion reactions (anti-histamine medications, corticosteroids and acetaminophen) (Local Consensus [5]).

Low Dose Chemotherapy and Stopping Immunosuppression

21. It is recommended to stop or minimize the CNI, and treat with low-dose cyclophosphamide and corticosteroids patients with:
    a. Evidence of persistent or progressive PTLD after reduction of immunosuppression
    b. PTLD refractory to rituximab monotherapy
    c. When PTLD is present with concurrent evidence of allograft rejection
    d. Fulminant PTLD

    (Local Consensus [5])

    Note 1: Low dose chemotherapy is effective without rituximab (Gross et al., 2005 [3a]), but may also be given concurrently with rituximab (Orjuela et al., 2003 [3b]).

    Note 2: CNI is frequently discontinued in liver and kidney recipients. CNI is often minimized in heart and intestinal recipients due to the relative rejection risk. (Local Consensus [5])

Conventional Dose Chemotherapy

22. It is recommended that patients with PTLD refractory to low-dose chemotherapy and patients with Burkitt lymphoma receive conventional-dose multi-agent chemotherapy (Local Consensus [5]).
    Note 1: Experience in adults with PTLD supports the use of multi-agent chemotherapy regimens (e.g., CHOP - cyclophosphamide, doxorubicin, vincristine, and prednisone) in patients with refractory PTLD after rituximab therapy (Choquet et al., 2007 [3b]).

    Note 2: Histology specific multi-agent chemotherapy regimens developed for pediatric patients should be used (Local Consensus [5]).

Supportive Care

23. It is recommended that all patients undergoing PTLD treatment have serum immunoglobulin G (IgG) levels monitored at monthly intervals, particularly in those receiving rituximab or chemotherapy (Local Consensus [5]).
24. It is recommended that intravenous immunoglobulin (IVIG) supplementation be given if hypogammaglobinemia (IgG<500) is detected in order to decrease risk of infection (Local Consensus [5]).

Post Therapy Monitoring

25. It is recommended that patients who have completely responded to therapy be monitored for recurrent PTLD and therapy-related complications such as hypogammaglobinemia, infection, bladder carcinoma, and graft health (Local Consensus [5]).
    Note 1: Monitoring might reasonably include blood EBV monitoring by PCR with surveillance radiographic studies as clinically indicated. Evidence supporting specific monitoring approaches is lacking.

    Note 2: A surveillance protocol used at Cincinnati Children's Hospital Medical Center (CCHMC) includes:

    - Every 2 week EBV monitoring by PCR for 3 months, then monthly during first year after cessation of therapy
    - Radiographic evaluation of previous sites of disease every 3 months for first year, every 4 months for second year, every 6 months for third year, then as clinically indicated
    - Yearly urinalysis (UA) monitoring for hematuria/proteinuria in patients that have received cyclophosphamide (Local Consensus [5])

Re-initiation of Immune Suppression

26. It is recommended to restart immunosuppression for patients responding to treatment:
    - Use T-cell antibody therapy such as muromonab-CD3 (OKT3) or antithymocyte globulin (ATG) with extreme caution in patients with PTLD or history of PTLD (Local Consensus [5]).
    - Restart calcineurin inhibitors at doses to achieve 50% of standard target level for the organ type and time since transplant in patients who have successfully responded to therapy without evidence of allograft rejection (Local Consensus [5]).
    - Consider the use of sirolimus when resuming immunosuppressive therapy because of the antiproliferative and autophagic role of mammalian target of rapamycin (mTOR) inhibition (Mathew, Kreis, & Friend, 2004 [2a]; Kirk et al., 2007 [4a]; Local Consensus [5]).

Prognosis

While the therapy for PTLD has a moderately high success rate, the prognosis for children that develop PTLD is guarded. Death due to infection or progressive PTLD remains a high concern. Comparison and interpretation of outcomes in published studies is hindered by studies with relatively small numbers of patients, different eras of transplantation therapy, few prospective studies, and lack of a uniform approach to diagnosis, definitions, monitoring and therapy. Many reports include both adult and pediatric populations. Some reported response rates for various therapeutic modalities in children are listed below.

- Reduction of immunosuppression alone yielded an objective response in 21 of 34 (62%) pediatric patients with PTLD (Hayashi et al., 2001 [4a]). Children responding to immunotherapy reduction were more likely to have polymorphic histology (16 of 17 patients, 94%) whereas only 29% of patients with monomorphic histology demonstrated an objective response.
- Reduction of immunosuppression combined with rituximab yielded a complete response (CR) in 9 of 16 (56%) pediatric patients with PTLD (Messahel et al., 2006 [4b]).
- Low dose chemotherapy with cyclophosphamide and prednisone yielded a 75% CR, 67% 2-year failure-free survival (FFS) in pediatric patients with PTLD that failed to respond to reduction of immunosuppression (Gross et al., 2005 [3a]).

Prognostic factors in PTLD are inconsistently defined or verified. Several studies in adults have identified elevated lactate dehydrogenase (LDH), multifocal lesions, and poor performance score as poor prognostic features. Other possible poor prognostic features in children include CNS or bone marrow involvement, monomorphic histology, EBV negative PTLD, and Burkitt lymphoma/leukemia.

Definitions:

Table of Evidence Levels

Quality Level	Definition
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5	Other: General review, expert opinion, case report, consensus report, or guideline

†a = good quality study; b = lesser quality study

Table of Recommendation Strength

Strength	Definition
"Strongly recommended"	There is consensus that benefits clearly outweigh risks and burdens (or vice-versa for negative recommendations).
"Recommended"	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is a lack of consensus to direct development of a recommendation.
Dimensions: In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.	
1. Grade of the body of evidence 2. Safety/harm 3. Health benefit to the patients (direct benefit) 4. Burden to patient of adherence to recommendation (cost, hassle, discomfort, pain, motivation, ability to adhere, time) 5. Cost-effectiveness to healthcare system (balance of cost/savings of resources, staff time, and supplies based on published studies or onsite analysis) 6. Directness (the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome]) 7. Impact on morbidity/mortality or quality of life	

Clinical Algorithm(s)

The following clinical algorithms are provided in the original guideline document:

- Post-Transplant Lymphoproliferative Disease (PTLD) Evaluation
- Treatment Algorithm for Epstein Barr virus (EBV)-associated PTLD

Scope

Disease/Condition(s)

Post-transplant lymphoproliferative disease (PTLD) following heart, kidney, liver and intestinal transplant

Guideline Category

Diagnosis

Evaluation

Management

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Hematology

Infectious Diseases

Pediatrics

Surgery

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Patients

Physician Assistants

Physicians

Guideline Objective(s)

To improve care by establishing consistent evidence-based care in the management of post-transplant lymphoproliferative disease (PTLD)

Target Population

Pediatric age recipients of heart, kidney, liver and intestinal transplant

Note: These guidelines are not intended for use in the following:

Non-transplant patients
Patients with Epstein Barr virus (EBV)-negative post-transplant lymphoproliferative disease (PTLD) (in tissue)
Patients with T cell PTLD
Patients with bone marrow transplant

Interventions and Practices Considered

Evaluation/Diagnosis

1. Confirmation of post-transplant lymphoproliferative disease (PTLD)
2. Laboratory screening and monitoring of Epstein Barr virus (EBV) serology
3. Monitoring of all patients for evidence of increased EBV-induced B-cell proliferation or EBV reactivation by measuring blood quantitative EBV polymerase chain reaction (PCR) at regular intervals after transplantation
4. Clinical assessment of symptoms that would indicate PTLD
5. Biopsy of organ/site once symptoms of PTLD are identified
    - In situ hybridization for Epstein Barr early response (EBER) performed on biopsy specimen
    - Additional diagnostic tests to determine extent of disease, including bone marrow, lumbar puncture, radiologic evaluation and endoscopy as indicated
6. Radiographic testing
    - Contrast enhanced computed tomography (CT)
    - Magnetic resonance imaging (MRI), fluorodeoxyglucose (FDG) positron emission tomography (PET), ultrasound, and chest radiographs as non-invasive follow-up

Management/Treatment

1. Preventive treatment for solid organ transplant recipients with detectable EBV deoxyribonucleic acid (DNA) in their blood
    - Maintenance of immunosuppression levels
    - Antiviral agents (e.g., ganciclovir, valganciclovir, acyclovir)

    - Rituximab (on an individual case basis)
2. PTLD treatment
    - PTLD staging and appropriate disease monitoring
    - Reduction of immunosuppression, including a decrease of calcineurin inhibitors and avoidance of anti-T cell monoclonal antibodies and alpha-interferon
    - Surgical resection of tumor mass
    - Rituximab
    - Low-dose chemotherapy and stopping immunosuppression
    - Conventional dose chemotherapy
    - Supportive care, including monitoring of serum IgG levels and intravenous immunoglobulin (IVIG) supplementation
3. Post therapy monitoring
4. Re-initiation of immune suppression

Major Outcomes Considered

- Morbidity and mortality
- Progression or regression of post-transplant lymphoproliferative disease (PTLD)

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

To select evidence for critical appraisal by the group for this guideline, the Medline, EMBASE and the Cochrane databases were searched for dates of February, 2003 to June, 2011 to generate an unrefined, "combined evidence" database using a search strategy focused on answering clinical questions relevant to Epstein Barr virus (EBV)/post-transplant lymphoproliferative disease (PTLD) and employing a combination of Boolean searching on human-indexed thesaurus terms (MeSH headings using an OVID Medline interface) and "natural language" searching on searching on human-indexed thesaurus terms (MeSH headings using an OVID Medline interface) and "natural language" searching on words in the title, abstract, and indexing terms. The citations were reduced by: eliminating duplicates, review articles, non-English articles, and adult articles. The resulting abstracts were reviewed by a methodologist to eliminate low quality and irrelevant citations. During the course of the guideline development, additional clinical questions were generated and subjected to the search process, and some relevant review articles were identified. February, 2003 was the last date for which literature was reviewed for the previous version of this guideline. The details of that review strategy are not documented. However, all previous citations were reviewed for appropriateness to this revision.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Table of Evidence Levels

Quality Level	Definition
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5	Other: General review, expert opinion, case report, consensus report, or guideline

†a = good quality study; b = lesser quality study

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The recommendations contained in this guideline were formulated by an interdisciplinary working group which performed systematic and critical literature reviews, using a grading scale, and examined current local clinical practices.

During formulation of these guidelines, the team members have remained cognizant of controversies and disagreements over the management of these patients. They have tried to resolve controversial issues by consensus where possible and, when not possible, to offer optional approaches to care in the form of information that includes best supporting evidence of efficacy for alternative choices.

Rating Scheme for the Strength of the Recommendations

Table of Recommendation Strength

Strength	Definition
"Strongly recommended"	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
"Recommended"	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is a lack of consensus to direct development of a recommendation.
Dimensions: In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.	
1. Grade of the body of evidence 2. Safety/harm 3. Health benefit to the patients (direct benefit) 4. Burden to patient of adherence to recommendation (cost, hassle, discomfort, pain, motivation, ability to adhere, time) 5. Cost-effectiveness to healthcare system (balance of cost/savings of resources, staff time, and supplies based on published studies or onsite analysis) 6. Directness (the extent to which the body of evidence directly answers the clinical question [population/problem, intervention,	

Strength	Definition
comparison, outcome]) 7. Impact on morbidity/mortality or quality of life	

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

The guidelines have been reviewed and approved by clinical experts not involved in the development process, distributed to senior management, and other individuals as appropriate to their intended purposes.

Evidence Supporting the Recommendations

References Supporting the Recommendations

Aris RM, Maia DM, Neuringer IP, Gott K, Kiley S, Gertis K, Handy J. Post-transplantation lymphoproliferative disorder in the Epstein-Barr virus-naive lung transplant recipient. Am J Respir Crit Care Med. 1996 Dec;154(6 Pt 1):1712-7. PubMed

Brenner DJ. Should we be concerned about the rapid increase in CT usage. Rev Environ Health. 2010 Jan-Mar;25(1):63-8. [10 references] PubMed

Broughton S, McClay JE, Murray A, Timmons C, Sommerauer J, Andrews W, Harkins P. The effectiveness of tonsillectomy in diagnosing lymphoproliferative disease in pediatric patients after liver transplantation. Arch Otolaryngol Head Neck Surg. 2000 Dec;126(12):1444-7. PubMed

Cacciarelli TV, Green M, Jaffe R, Mazariegos GV, Jain A, Fung JJ, Reyes J. Management of posttransplant lymphoproliferative disease in pediatric liver transplant recipients receiving primary tacrolimus (FK506) therapy. Transplantation. 1998 Oct 27;66(8):1047-52. PubMed

Cao S, Cox K, Esquivel CO, Berquist W, Concepcion W, Ojogho O, Monge H, Krams S, Martinez O, So S. Posttransplant lymphoproliferative disorders and gastrointestinal manifestations of Epstein-Barr virus infection in children following liver transplantation. Transplantation. 1998 Oct 15;66(7):851-6. PubMed

Cesaro S, Murrone A, Mengoli C, Pillon M, Biasolo MA, Calore E, Tridello G, Varotto S, Alaggio R, Zanesco L, Palu G, Messina C. The real-time polymerase chain reaction-guided modulation of immunosuppression enables the pre-emptive management of Epstein-Barr virus reactivation after allogeneic haematopoietic stem cell transplantation. Br J Haematol. 2005 Jan;128(2):224-33. PubMed

Chadburn A, Cesarman E, Liu YF, Addonizio L, Hsu D, Michler RE, Knowles DM. Molecular genetic analysis demonstrates that multiple posttransplantation lymphoproliferative disorders occurring in one anatomic site in a single patient represent distinct primary lymphoid neoplasms. Cancer. 1995 Jun 1;75(11):2747-56. PubMed

Choquet S, Leblond V, Herbrecht R, Socie G, Stoppa AM, Vandenberghe P, Fischer A, Morschhauser F, Salles G, Feremans W, Vilmer E, Peraldi MN, Lang P, Lebranchu Y, Oksenhendler E, Garnier JL, Lamy T, Jaccard A, Ferrant A, Offner F, Hermine O, Moreau A, Fafi-Kremer S, Morand P, Chatenoud L, Berriot-Varoqueaux N, Bergougnoux L, Milpied N. Efficacy and safety of rituximab in B-cell post-

transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. Blood. 2006 Apr 15;107(8):3053-7. PubMed

Choquet S, Trappe R, Leblond V, Jager U, Davi F, Oertel S. CHOP-21 for the treatment of post-transplant lymphoproliferative disorders (PTLD) following solid organ transplantation. Haematologica. 2007 Feb;92(2):273-4. PubMed

Cohen JI. Epstein-Barr virus lymphoproliferative disease associated with acquired immunodeficiency. Medicine (Baltimore). 1991 Mar;70(2):137-60. [139 references] PubMed

D'Antiga L, Del Rizzo M, Mengoli C, Cillo U, Guariso G, Zancan L. Sustained Epstein-Barr virus detection in paediatric liver transplantation. Insights into the occurrence of late PTLD. Liver Transpl. 2007 Mar;13(3):343-8. PubMed

Dharnidharka VR, Araya CE. Post-transplant lymphoproliferative disease. Pediatr Nephrol. 2009 Apr;24(4):731-6. PubMed

Dodd GD 3rd, Ledesma-Medina J, Baron RL, Fuhrman CR. Posttransplant lymphoproliferative disorder: intrathoracic manifestations. Radiology. 1992 Jul;184(1):65-9. PubMed

Donnelly LF, Frush DP, Marshall KW, White KS. Lymphoproliferative disorders: CT findings in immunocompromised children. AJR Am J Roentgenol. 1998 Sep;171(3):725-31. PubMed

Fafi-Kremer S, Brengel-Pesce K, Bargues G, Bourgeat MJ, Genoulaz O, Seigneurin JM, Morand P. Assessment of automated DNA extraction coupled with real-time PCR for measuring Epstein-Barr virus load in whole blood, peripheral mononuclear cells and plasma. J Clin Virol. 2004 Jun;30(2):157-64. PubMed

Genetech. Rituxan. South San Francisco (CA): Genetech; 2010.

Gonzalez-Barca E, Domingo-Domenech E, Capote FJ, Gomez-Codina J, Salar A, Bailen A, Ribera JM, Lopez A, Briones J, Munoz A, Encuentra M, de Sevilla AF, GEL/TAMO (Grupo Espanol de Linfomas), GELCAB (Grupo para el Estudio de los Linfomas Catalano-Balear), GOTEL (Grupo Oncologico para el Tratamiento y Estudio de los Linfomas). Prospective phase II trial of extended treatment with rituximab in patients with B-cell post-transplant lymphoproliferative disease. Haematologica. 2007 Nov;92(11):1489-94. PubMed

Green M, Michaels MG, Webber SA, Rowe D, Reyes J. The management of Epstein-Barr virus associated post-transplant lymphoproliferative disorders in pediatric solid-organ transplant recipients. Pediatr Transplant. 1999 Nov;3(4):271-81. [40 references] PubMed

Groen P, Witte D. Quantitative EBV assay using the LightCycler instrument to onitor transplant patients at risk for PTLD. Pediatr Dev Pathol. 2001;4(4):414-5.

Gross TG, Bucuvalas JC, Park JR, Greiner TC, Hinrich SH, Kaufman SS, Langnas AN, McDonald RA, Ryckman FC, Shaw BW, Sudan DL, Lynch JC. Low-dose chemotherapy for Epstein-Barr virus-positive post-transplantation lymphoproliferative disease in children after solid organ transplantation. J Clin Oncol. 2005 Sep 20;23(27):6481-8. PubMed

Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, Lister TA, Bloomfield CD. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol. 1999 Dec;17(12):3835-49. PubMed

Harwood JS, Gould FK, McMaster A, Hamilton JR, Corris PA, Hasan A, Gennery AR, Dark JH. Significance of Epstein-Barr virus status and post-transplant lymphoproliferative disease in pediatric thoracic transplantation. Pediatr Transplant. 1999 May;3(2):100-3. PubMed

Hayashi RJ, Kraus MD, Patel AL, Canter C, Cohen AH, Hmiel P, Howard T, Huddleston C, Lowell JA, Mallory G Jr, Mendeloff E,

Molleston J, Sweet S, DeBaun MR. Posttransplant lymphoproliferative disease in children: correlation of histology to clinical behavior. J Pediatr Hematol Oncol. 2001 Jan;23(1):14-8. PubMed

Herth FJ, Becker HD. Transthoracic ultrasound. Respiration. 2003 Jan-Feb;70(1):87-94. [43 references] PubMed

Heslop HE, Slobod KS, Pule MA, Hale GA, Rousseau A, Smith CA, Bollard CM, Liu H, Wu MF, Rochester RJ, Amrolia PJ, Hurwitz JL, Brenner MK, Rooney CM. Long-term outcome of EBV-specific T-cell infusions to prevent or treat EBV-related lymphoproliferative disease in transplant recipients. Blood. 2010 Feb 4;115(5):925-35. PubMed

Hirsch W, Sorge I, Krohmer S, Weber D, Meier K, Till H. MRI of the lungs in children. Eur J Radiol. 2008 Nov;68(2):278-88. [26 references] PubMed

Ho M, Jaffe R, Miller G, Breinig MK, Dummer JS, Makowka L, Atchison RW, Karrer F, Nalesnik MA, Starzl TE. The frequency of Epstein-Barr virus infection and associated lymphoproliferative syndrome after transplantation and its manifestations in children. Transplantation. 1988 Apr;45(4):719-27. PubMed

Hoffmann M, Kletter K, Diemling M, Becherer A, Pfeffel F, Petkov V, Chott A, Raderer M. Positron emission tomography with fluorine-18-2-fluoro-2-deoxy-D-glucose (F18-FDG) does not visualize extranodal B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT)-type. Ann Oncol. 1999 Oct;10(10):1185-9. PubMed

Holmes RD, Orban-Eller K, Karrer FR, Rowe DT, Narkewicz MR, Sokol RJ. Response of elevated Epstein-Barr virus DNA levels to therapeutic changes in pediatric liver transplant patients: 56-month follow up and outcome. Transplantation. 2002 Aug 15;74(3):367-72. PubMed

Inomata Y, Hamamoto R, Yoshimoto K, Zeledon M. [Current status and perspective of pediatric liver transplantation in Japan]. Nippon Rinsho. 2005 Nov;63(11):1986-92. [15 references] PubMed

Kingma DW, Shad A, Tsokos M, Fest T, Otsuki T, Frekko K, Werner E, Werner A, Magrath I, Raffeld M, Jaffe ES. Epstein-Barr virus (EBV)-associated smooth-muscle tumor arising in a post-transplant patient treated successfully for two PT-EBV-associated large-cell lymphomas. Case report. Am J Surg Pathol. 1996 Dec;20(12):1511-9. PubMed

Kirk AD, Cherikh WS, Ring M, Burke G, Kaufman D, Knechtle SJ, Potdar S, Shapiro R, Dharnidharka VR, Kauffman HM. Dissociation of depletional induction and posttransplant lymphoproliferative disease in kidney recipients treated with alemtuzumab. Am J Transplant. 2007 Nov;7(11):2619-25. PubMed

Kullberg-Lindh C, Olofsson S, Brune M, Lindh M. Comparison of serum and whole blood levels of cytomegalovirus and Epstein-Barr virus DNA. Transpl Infect Dis. 2008 Oct;10(5):308-15. PubMed

Lattyak BV, Rosenthal P, Mudge C, Roberts JP, Renze JF, Osorio RW, Emond JC, Lalwani AK. Posttransplant lymphoproliferative disorder presenting in the head and neck. Laryngoscope. 1998 Aug;108(8 Pt 1):1195-8. PubMed

Lee TC, Savoldo B, Rooney CM, Heslop HE, Gee AP, Caldwell Y, Barshes NR, Scott JD, Bristow LJ, O'Mahony CA, Goss JA. Quantitative EBV viral loads and immunosuppression alterations can decrease PTLD incidence in pediatric liver transplant recipients. Am J Transplant. 2005 Sep;5(9):2222-8. PubMed

Lopez-Ben R, Smith JK, Kew CE 2nd, Kenney PJ, Julian BA, Robbin ML. Focal posttransplantation lymphoproliferative disorder at the renal allograft hilum. AJR Am J Roentgenol. 2000 Nov;175(5):1417-22. PubMed

Markin RS. Manifestations of Epstein-Barr virus-associated disorders in liver. Liver. 1994 Feb;14(1):1-13. PubMed

Marom EM, McAdams HP, Butnor KJ, Coleman RE. Positron emission tomography with fluoro-2-deoxy-D-glucose (FDG-PET) in the staging of post transplant lymphoproliferative disorder in lung transplant recipients. J Thorac Imaging. 2004 Apr;19(2):74-8. PubMed

Mathew T, Kreis H, Friend P. Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies. Clin Transplant. 2004 Aug;18(4):446-9. PubMed

Maturen KE, Blane CE, Strouse PJ, Fitzgerald JT. Pulmonary involvement in pediatric lymphoma. Pediatr Radiol. 2004 Feb;34(2):120-4. PubMed

McCormack L, Hany TI, Hubner M, Petrowsky H, Mullhaupt B, Knuth A, Stenner F, Clavien PA. How useful is PET/CT imaging in the management of post-transplant lymphoproliferative disease after liver transplantation. Am J Transplant. 2006 Jul;6(7):1731-6. PubMed

McDiarmid SV, Jordan S, Kim GS, Toyoda M, Goss JA, Vargas JH, Martin MG, Bahar R, Maxfield AL, Ament ME, Busuttil RW, Lee GS. Prevention and preemptive therapy of postransplant lymphoproliferative disease in pediatric liver recipients. Transplantation. 1998 Dec 27;66(12):1604-11. PubMed

Meerbach A, Wutzler P, Hafer R, Zintl F, Gruhn B. Monitoring of Epstein-Barr virus load after hematopoietic stem cell transplantation for early intervention in post-transplant lymphoproliferative disease. J Med Virol. 2008 Mar;80(3):441-54. PubMed

Messahel B, Taj MM, Hobson R, Hadzic N, Ramsay A, Hann I, Pinkerton R. Single agent efficacy of rituximab in childhood immunosuppression related lymphoproliferative disease: a United Kingdom Children's Cancer Study Group (UKCCSG) retrospective review. Leuk Lymphoma. 2006 Dec;47(12):2584-9. PubMed

O'Conner AR, Franc BL. FDG PET imaging in the evaluation of post-transplant lymphoproliferative disorder following renal transplantation. Nucl Med Commun. 2005 Dec;26(12):1107-11. PubMed

Okano M, Gross TG. Epstein-Barr virus-associated hemophagocytic syndrome and fatal infectious mononucleosis. Am J Hematol. 1996 Oct;53(2):111-5. [38 references] PubMed

Orjuela M, Gross TG, Cheung YK, Alobeid B, Morris E, Cairo MS. A pilot study of chemoimmunotherapy (cyclophosphamide, prednisone, and rituximab) in patients with post-transplant lymphoproliferative disorder following solid organ transplantation. Clin Cancer Res. 2003 Sep 1;9(10 Pt 2):3945S-52S. PubMed

Perry C, Herishanu Y, Metzer U, Bairey O, Ruchlemer R, Trejo L, Naparstek E, Sapir EE, Polliack A. Diagnostic accuracy of PET/CT in patients with extranodal marginal zone MALT lymphoma. Eur J Haematol. 2007 Sep;79(3):205-9. PubMed

Pickhardt PJ, Siegel MJ, Anderson DC, Hayashi R, DeBaun MR. Chest radiography as a predictor of outcome in posttransplantation lymphoproliferative disorder in lung allograft recipients. AJR Am J Roentgenol. 1998 Aug;171(2):375-82. PubMed

Pickhardt PJ, Siegel MJ. Posttransplantation lymphoproliferative disorder of the abdomen: CT evaluation in 51 patients. Radiology. 1999 Oct;213(1):73-8. PubMed

Piriou ER, van Dort K, Nanlohy NM, Miedema F, van Oers MH, van Baarle D. Altered EBV viral load setpoint after HIV seroconversion is in accordance with lack of predictive value of EBV load for the occurrence of AIDS-related non-Hodgkin lymphoma. J Immunol. 2004 Jun 1;172(11):6931-7. PubMed

Preiksaitis JK, Pang XL, Fox JD, Fenton JM, Caliendo AM, Miller GG, American Society of Transplantation Infectious Diseases Community of Practice. Interlaboratory comparison of epstein-barr virus viral load assays. Am J Transplant. 2009 Feb;9(2):269-79. PubMed

Quintanilla-Martinez L, Kumar S, Fend F, Reyes E, Teruya-Feldstein J, Kingma DW, Sorbara L, Raffeld M, Straus SE, Jaffe ES. Fulminant EBV(+) T-cell lymphoproliferative disorder following acute/chronic EBV infection: a distinct clinicopathologic syndrome. Blood. 2000 Jul 15;96(2):443-51. PubMed

Randhawa PS, Magnone M, Jordan M, Shapiro R, Demetris AJ, Nalesnik M. Renal allograft involvement by Epstein-Barr virus associated post-transplant lymphoproliferative disease. Am J Surg Pathol. 1996 May;20(5):563-71. PubMed

Riebel T, Kebelmann-Betzing C, Scheer I. Ultrasound in abdominal and soft-tissue childhood PTLD (post-transplant lymphoproliferative disease). Ultraschall Med. 2007 Apr;28(2):201-5. PubMed

Robbins E. Radiation risks from imaging studies in children with cancer. Pediatr Blood Cancer. 2008 Oct;51(4):453-7. [15 references] PubMed

Rogers BB, Sommerauer J, Quan A, Timmons CF, Dawson DB, Scheuermann RH, Krisher K, Atkins C. Epstein-Barr virus polymerase chain reaction and serology in pediatric post-transplant lymphoproliferative disorder: three-year experience. Pediatr Dev Pathol. 1998 Nov-Dec;1(6):480-6. PubMed

Rowe DT, Qu L, Reyes J, Jabbour N, Yunis E, Putnam P, Todo S, Green M. Use of quantitative competitive PCR to measure Epstein-Barr virus genome load in the peripheral blood of pediatric transplant patients with lymphoproliferative disorders. J Clin Microbiol. 1997 Jun;35(6):1612-5. PubMed

Roy S, Vivero RJ, Smith LP. Adenotonsillar pathology in post-transplant patients. Int J Pediatr Otorhinolaryngol. 2008 Jun;72(6):865-8. PubMed

Sarkar S, Selvaggi G, Mittal N, Cenk Acar B, Weppler D, Kato T, Tzakis A, Ruiz P. Gastrointestinal tract ulcers in pediatric intestinal transplantation patients: etiology and management. Pediatr Transplant. 2006 Mar;10(2):162-7. PubMed

Schubert S, Abdul-Khaliq H, Lehmkuhl HB, Yegitbasi M, Reinke P, Kebelmann-Betzig C, Hauptmann K, Gross-Wieltsch U, Hetzer R, Berger F. Diagnosis and treatment of post-transplantation lymphoproliferative disorder in pediatric heart transplant patients. Pediatr Transplant. 2009 Feb;13(1):54-62. PubMed

Sebelin-Wulf K, Nguyen TD, Oertel S, Papp-Vary M, Trappe RU, Schulzki A, Pezzutto A, Riess H, Subklewe M. Quantitative analysis of EBV-specific CD4/CD8 T cell numbers, absolute CD4/CD8 T cell numbers and EBV load in solid organ transplant recipients with PLTD. Transpl Immunol. 2007 Apr;17(3):203-10. PubMed

Shapiro RS, McClain K, Frizzera G, Gajl-Peczalska KJ, Kersey JH, Blazar BR, Arthur DC, Patton DF, Greenberg JS, Burke B, et al.. Epstein-Barr virus associated B cell lymphoproliferative disorders following bone marrow transplantation. Blood. 1988 May;71(5):1234-43. PubMed

Smets F, Bodeus M, Goubau P, Reding R, Otte JB, Buts JP, Sokal EM. Characteristics of Epstein-Barr virus primary infection in pediatric liver transplant recipients. J Hepatol. 2000 Jan;32(1):100-4. PubMed

Srivastava T, Zwick DL, Rothberg PG, Warady BA. Posttransplant lymphoproliferative disorder in pediatric renal transplantation. Pediatr Nephrol. 1999 Nov;13(9):748-54. PubMed

Stevens SJ, Verschuuren EA, Verkuujlen SA, Van Den Brule AJ, Meijer CJ, Middeldorp JM. Role of Epstein-Barr virus DNA load monitoring in prevention and early detection of post-transplant lymphoproliferative disease. Leuk Lymphoma. 2002 Apr;43(4):831-40. [91 references] PubMed

von Falck C, Maecker B, Schirg E, Boerner AR, Knapp WH, Klein C, Galanski M. Post transplant lymphoproliferative disease in pediatric solid organ transplant patients: a possible role for [18F]-FDG-PET(/CT) in initial staging and therapy monitoring. Eur J Radiol. 2007 Sep;63(3):427-35. PubMed

Walker RC, Paya CV, Marshall WF, Strickler JG, Wiesner RH, Velosa JA, Habermann TM, Daly RC, McGregor CG. Pretransplantation seronegative Epstein-Barr virus status is the primary risk factor for posttransplantation lymphoproliferative disorder in adult heart, lung, and other solid organ transplantations. J Heart Lung Transplant. 1995 Mar-Apr;14(2):214-21. PubMed

Webber SA, Naftel DC, Fricker FJ, Olesnevich P, Blume ED, Addonizio L, Kirklin JK, Canter CE, Pediatric Heart Transplant Study. Lymphoproliferative disorders after paediatric heart transplantation: a multi-institutional study. Lancet. 2006 Jan 21;367(9506):233-9. PubMed

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Effective medical management of post-transplant lymphoproliferative disease (PTLD) in pediatric age recipients of heart, kidney, liver and intestinal transplant

Potential Harms

- It is important to take into account the relative risk of morbidity and/or mortality due to rejection, secondary to decreased immunosuppression for each specific organ type and patient.
- It is recommended that patients who have completely responded to therapy be monitored for recurrent post-transplant lymphoproliferative disease (PTLD) and therapy-related complications such as hypogammaglobinemia, infection, bladder carcinoma, and graft health
- Caretakers need to be aware of the ongoing risk of high cumulative doses of radiation and contrast material from imaging studies performed for the detection and treatment of PTLD

Contraindications

Contraindications

It is recommended to avoid use of:

- Anti-T cell monoclonocal antibodies when possible in patients with post-transplant lymphoproliferative disease (PTLD)
- Alpha-interferon as a first line therapy due to concerns of toxicity and availability of newer agents.

Qualifying Statements

Qualifying Statements

- While the therapy for post-transplant lymphoproliferative disease (PTLD) has a moderately high success rate, the prognosis for children that develop PTLD is guarded. Death due to infection or progressive PTLD remains a high concern. Comparison and interpretation of outcomes in published studies is hindered by studies with relatively small numbers of patients, different eras of transplantation therapy, few prospective

studies, and lack of a uniform approach to diagnosis, definitions, monitoring and therapy. Many reports include both adult and pediatric populations.

- These recommendations result from review of literature and practices current at the time of their formulations. This protocol does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the guidelines to meet the specific and unique requirements of individual patients. Adherence to this pathway is voluntary. The physician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

Implementation of the Guideline

Description of Implementation Strategy

Appropriate companion documents have been developed to assist in the effective dissemination and implementation of the guideline.

Implementation Tools

Chart Documentation/Checklists/Forms

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Cincinnati Children's Hospital Medical Center. Evidence based clinical practice guideline for management of EBV-associated post-transplant lymphoproliferative disease (PTLD) in solid organ transplant. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2012 Jan. 18 p. [110 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Jun (revised Jan 2012)

Guideline Developer(s)

Cincinnati Children's Hospital Medical Center - Hospital/Medical Center

Source(s) of Funding

Cincinnati Children's Hospital Medical Center

Guideline Committee

Epstein Barr Virus (EBV) Work Group, Cincinnati Children's Hospital Medical Center

Composition of Group That Authored the Guideline

Team Members 2008-2011: Nada Yazigi, MD, Gastroenterology, Hepatology, & Nutrition; Michael Absalon, MD, PhD, Hematology/Oncology; Alan Brody, MD, Radiology; Jens Goebel, MD, Division of Nephrology; Trina Hemmelgarn, PharmD, Division of Pharmacy; Robert Spicer, MD, Cardiology; Karen Uzark, PhD, CPNP, Cardiology; David Witte, MD, Pathology

James M. Anderson Center for Health Systems Excellence: Eloise Clark, MPH, MBA, Guidelines Program Administrator, Evidence Facilitator; Danette Stanko-Lopp, MA, MPH, Epidemiologist; Karen Vonderhaar, MS, RN, Guidelines Program Administrator, Methodologist

Ad Hoc Advisors: Rebecca Brady, MD, Division of Infectious Disease; John Bucuvalas, MD, Gastroenterology, Hepatology, & Nutrition; John Perentesis, MD, Hematology/Oncology; Tom Gross, MD, Division of Hematology/Oncology, Nationwide Hospital; Catherine Bollard, MBChB, MD, Associate Professor of Pediatrics, Medicine, and Immunology, Center for Cell and Gene Therapy Baylor College of Medicine; Michael Green, MD, MPH, Professor of Pediatrics, Surgery & Clinical and Translational Science, University of Pittsburgh School of Medicine Division of Infectious Diseases, Children's Hospital of Pittsburgh; Susan Prockop, MD, Assistant Attending, Pediatric Bone Marrow Transplant Service, Department of Pediatrics, Memorial Sloan-Kettering Cancer Center

Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Cincinnati Children's Hospital Medical Center. Evidence based clinical practice guideline for management of EBV-associated post-transplant lymphoproliferative disease (PTLD) in solid organ transplant. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2011 Jun. 18 p. [103 references]

Guideline Availability

Electronic copies: Available from the Cincinnati Children's Hospital Medical Center Web site .

Print copies: For information regarding the full-text guideline, print copies, or evidence-based practice support services contact the Cincinnati Children's Hospital Medical Center Health James M. Anderson Center for Health Systems Excellence at EBDMInfo@cchmc.org.

Availability of Companion Documents

The following are available:

- Evidence-based care guideline development and update process. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2006 Mar. 35 p. Available in Portable Document Format (PDF) from the Cincinnati Children's Hospital Medical Center .
- Table of evidence levels. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2009 May 7. 1 p. Available from the Cincinnati Children's Hospital Medical Center .
- Grading a body of evidence to answer a clinical question. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2009 May 7. 1 p. Available from the Cincinnati Children's Hospital Medical Center .
- Judging the strength of a recommendation. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2009 May 7. 1 p. Available from the Cincinnati Children's Hospital Medical Center .

Print copies: For information regarding the full-text guideline, print copies, or evidence-based practice support services contact the Cincinnati Children's Hospital Medical Center Health James M. Anderson Center for Health Systems Excellence at EBDMInfo@cchmc.org.

A post-transplant lymphoproliferative disease clinical checklist is available as an addendum to the original guideline document .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on March 11, 2004. This summary was updated by ECRI on January 12, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Rituxan (Rituximab). This summary was updated by ECRI Institute on October 8, 2008 following the U.S. Food and Drug Administration advisory on Rituxan (rituximab). This NGC summary was updated by ECRI Institute on November 21, 2011. This NGC summary was updated by ECRI Institute on October 17, 2012. This summary was updated by ECRI Institute on October 28, 2013 following the U.S. Food and Drug Administration advisory on Acetaminophen. This summary was updated by ECRI Institute on November 21, 2013 following the U.S. Food and Drug Administration advisory on Arzerra (ofatumumab) and Rituxan (rituximab).

Copyright Statement

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.